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| 09/863,803  | 05/22/2001  | Jeffrey J. Rade      | 71699/55591         | 8907             |
| 21874   | 7590        | 03/30/2005           | EXAMINER            |                  |
| EDWARDS & ANGELL, LLP<br>P.O. BOX 55874<br>BOSTON, MA 02205 |             |                      | LI, QIAN JANICE     |                  |
|   |             |                      | ART UNIT            | PAPER NUMBER     |

1632

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/863,803

Applicant(s)

RADE ET AL.

Examiner

Q. Janice Li

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 11 January 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 29-67 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 29-67 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 May 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 1/11/05.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/11/2005 has been entered.

The amendment and response filed 1/11/05 have been entered. Claims 29, 30 have been amended. Claims 52-67 are newly submitted. Claims 29-67 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification as originally filed does not describe the invention as now claimed.

The amended and newly submitted independent claims 29, 30, 52, 56, 59

(submitted 6/29/04 and 1/11/05) recite, "the functional fragment of the TM has at least about 85% of the protein C binding activity of human thrombomodulin". However, the specification as originally filed fails to specify the range and degree of the protein C binding activity for TM fragments. Further, applicants failed to specifically point out where in the specification the support for the amendment could be found. Accordingly, the amendment is an addition to the disclosure as originally filed, and introduced new matter into the specification.

Claim 29 or 52, or 56, or 59 recites "early graft failure", which graft encompasses any organ and tissue graft, not limited to "vascular graft" as originally disclosed. As such, the amendment broadens the scope of the invention. Further, applicants failed to specifically point out where in the specification the support for the amendment could be found. Applicants are reminded that the original disclosure is entitled "Genetic engineering of vascular grafts to resist disease", and throughout the specification, vascular graft is consistently the subject of the graft. The original disclosure is silent concerning other types of graft failure. Accordingly, the amendment improperly broadened the scope of the invention and introduced new matter into the specification.

MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS

FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added). Since the amendment has added or improperly broadened the scope of the original disclosure, the amendment is a departure from or an addition to the disclosure of the application as filed, thus it introduces new matter into the disclosure.

For reasons set forth above, the amendments filed 1/11/05 and 6/29/04 are objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action. Alternatively, Applicant are invited to specifically point out where in the specification the support can be found for the amendment made to the disclosure.

#### WRITTEN DESCRIPTION REQUIREMENT

The previous rejection under this provision concerning the subject matter, "functional fragments of TM, EPCR, and NF-kB inhibitor" is withdrawn in view of claim amendment, last paragraph, page 20 of the specification, and exhibit submitted with respect to art known functional fragments of TM and EPCR. The references of the exhibit are listed in the specification as originally filed.

#### ENABLEMENT REQUIREMENT

The previous rejection under this provision concerning claim recitation, “functional fragments of TM, EPCR, and NF-kB inhibitor” is withdrawn in view of claim amendment, last paragraph, page 20 of the specification, and exhibit submitted with respect to art known functional fragments of TM and EPCR.

Claims 29-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a mammal to resist early vascular graft failure using autologous vascular graft, does not reasonably provide enablement for doing so using allogenic or xenogenic vascular graft. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given broadest reasonable interpretation, the claims encompass transplanting a vascular graft from an allogenic or xenogenic source, wherein the graft could resist early graft failure. The specification teaches that using *ex vivo* approach, a replication defective adenoviral vector encoding TM, EPCR, or I $\kappa$ B were introduced into rabbit vascular grafts, and expressed *in vivo* for up to 42 days after implantation, that such procedure reduced bound thrombin activity, and increased the ability for endothelial cells to generate APC (example 5 and fig. 10); wherein the vascular graft is obtained from jugular vein of a rabbit, and transplanted to carotid artery of the same rabbit (Specification, example 1). The specification is silent regarding the consequence of implanting a allogenic or xenogenic vascular graft, and whether the increased APC could resist early graft failure in allogenic or xenogenic vascular grafts. Thus, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

With regard to allogenic and xenogenic graft transplantation, there are still major barriers for successful transplantation as of post-filing dates. *Game et al* (Wien Klin Wochenschr 2001;113:823-38) detailed different types of allogenic and xenogenic rejection (hyperacute, acute, chronic) and underlying mechanisms involving multiple pathways that lead to the failure of allogenic and xenogenic transplantation, and states, "WHILE MAJOR IMPROVEMENTS HAVE BEEN MADE IN THE PREVENTION AND TREATMENT OF HYPERACUTE AND ACUTE TRANSPLANT REJECTION, MOST GRAFTS WILL SUCCUMB TO CHRONIC REJECTION: THIS REFLECTS THE EXTENT OF OUR KNOWLEDGE OF THE MECHANISMS THAT DRIVE THESE PROCESSES", as for xenotransplantation, "NOVEL APPROACHES HAVE OVERCOME SOME

EARLY ANTIBODY MEDIATED REJECTION EVENTS BUT THEN REVEAL A HUGE, INTENSE, ADAPTIVE CELLULAR RESPONSE". *Platt et al* (Nat Biotech 2002 Mar;20(3)231-2) teach, "UNFORTUNATELY, SOLVING THE PROBLEM OF HYPERACUTE REJECTION DOES NOT MAKE XENOTRANSPLANTATION FEASIBLE, BUT RATHER REVEALS A MORE VEXING PROBLEM CALLED ACUTE VASCULAR REJECTION. ACUTE VASCULAR REJECTION, LIKE HYPERACUTE REJECTION, IS TRIGGERED BY ANTI-DONOR ANTIBODIES; HOWEVER, IN CONTRAST TO HYPERACUTE REJECTION, THESE ANTIBODIES ARE NOT DIRECTED EXCLUSIVELY AGAINST  $\alpha 1,3$  GAL, AND THE INVOLVEMENT OF THE COMPLEMENT SYSTEM IS FAR MORE SUBTLE". The specification fails to teach whether the increased APC activation according to instantly claimed invention could resist such robust rejection mechanism, and given the common knowledge of the skill, it is highly unlikely that the increased APC could resist early graft failure for allogeneic and xenogenic transplantation. It would have required undue experimentation for the skilled artisan intending to practice the instant invention.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29, 31-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29, 31-67 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. In the instant case, the omitted element is the step of introducing a genetically modified graft into the mammal. This is because the method provides for treating a mammal, wherein the step comprises introducing into graft cells *ex vivo* at least one nucleic acid encoding a therapeutic agent, however, there is no step that such genetically modified graft has been introduced into the mammal, and consequence of grafting, which would clearly relate back to the preamble. Steps b and c of the method simply state the behavior and consequence of the introduced nucleic acids, which are not a positive step by the hands of man. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claim 34 recites the limitation "vascular graft". There is insufficient antecedent basis for this limitation in the claim.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Waugh et al* (Circ Res 1999;84:84-92, IDS).

Claim 51 is drawn to a kit comprising agents for increasing APC, means for detecting cell expression of the agents, means for detecting the increased APC in the blood vessel, and directions for using the kit.

*Waugh et al* teach an agent that increases APC, i.e. an adenoviral vector encoding TM (column 1, page 85), means and instructions for detecting cell expression of the TM and activated protein C (column 2, page 85). Although *Waugh et al* do not explicitly teach a kit comprising all of the above elements; it is a common knowledge in the art to assemble a kit including aforementioned elements for the ease of commercial activity.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to gather all the agents and instructions as taught by *Waugh et al* and assemble them in the form of a kit with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for the ease of conducting experiments or trade. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

It is noted that claim limitation "for performing the methods of claims 29 or 30" carries little weight in determining the novelty of the kit. This is because that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand alone. The MPEP states that in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art." *In re Casey*, 152 USPQ 235 (CCPA 1967); *In re Otto*, 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02).

Claim 51 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Esmon et al* (US 5,804,392) or *Fukudome et al* (US 5,852,171).

*Esmon et al* teach an agent that increases APC, e.g. plasma EPCR (column 1, page 85), and nucleic acid encoding EPCR (column 7), means and instructions for detecting cell expression of the EPCR and activated protein C (abstract, claims, and fig. 4D). Although *Esmon et al* do not explicitly teach a kit comprising all of the above elements; it is a common knowledge in the art to assemble a kit for the ease of commercial activity.

*Fukudome et al* teach an agent that increases APC, e.g. nucleic acid encoding EPCR (e.g. column 9), means and instructions for detecting cell expression of the EPCR and activated protein C (figs. 2a-d, and fig. 3). Although *Fukudome et al* do not explicitly teach a kit comprising all of the above elements; it is a common knowledge in the art to assemble a kit for the ease of commercial activity.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to gather all the agents and instructions as taught by *Esmon et al* or *Fukudome* and present them in the form of a kit with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so for the ease of experiment or trade. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 29-50, 52, 59, 60, 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Vassalli et al* (Cardiovasc Res 1997;35:459-69), in view of *Waugh et al* (Circ Res 1999;84:84-92, IDS) and *Thomas et al* (Transplant 1999;68:1660-73).

These claims are directed to a method for treating a mammal to resist early vascular graft failure by introducing to a vascular graft an effective amount of a nucleic acid encoding a thrombomodulin (TM), wherein the nucleic acid further encodes a NF- $\kappa$ B inhibitor (I $\kappa$ B). The specification teaches that early graft failure is typically due to occlusive *thrombosis* (Specification, page 1, last paragraph and claim 37).

*Vassalli et al* teach that conventional antithrombotic treatment is not uniformly successful and is associated with hemorrhagic side effects. Gene therapy could be a potential alternative because its unique ability to express an antithrombotic gene at selected sites of the vessel wall. *Vassalli et al* go on to teach this approach may be used in clinical conditions such as coronary artery bypass (§ 2.2) and vascular grafts (§ 2.7) either directly *in vivo* or *ex vivo* prior to cell transplant (e.g. abstract), and thrombomodulin is one of the therapeutic gene of choice for such gene therapy strategy (table 1). *Vassalli et al* also pointed to the success of decreased thrombus formation using adenoviral vector expressing TM in human endothelial cells *in vitro* (paragraph bridging pages 464-5). *Vassalli et al* do not actually show that adenoviral vector expressing TM would suppress vascular thrombosis *in vivo*.

*Waugh et al* supplemented the teaching of *Vassalli et al* by illustrating the success of expressing TM in the injured segment of vessel wall on inhibiting thrombosis in an animal model. *Waugh et al* constructed an adenoviral vector encoding the TM

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operably linked to a Rous sarcoma virus ITR promoter, and delivered such locally to exposed common femoral artery. *Waugh et al* teach because it is impossible to precisely evaluate local TM levels *in vivo*, they monitored the formation of vascular thrombus *in vivo* as a functional assay for expression of TM. Vascular samples were collected six days after the adenoviral vector delivery and three days after initiation of the thrombosis, which clearly showed that local over-expression of TM via the Adv-TM nucleic acids is sufficient for preventing and treating *in vivo* arterial thrombus formation (page 88, and fig.5), which indirectly evidenced that the protein C activation has lasted at least one or two days. *Waugh et al* also measures APC to show the correlation between activation of protein C and TM overexpression in endothelial cells *in vitro*. Figure 3 shows that Adv/RSV-TM construct was able to produce APC at a level 153% of controls. Although *Waugh et al* do not use a model of vascular graft, the vascular injury model generated a process of thrombosis, and the extensive manipulation of the vessels in the vascular injury model (artery exposure, ligation, cannulation, division, isolation from circulation, clamping, etc.) simulates the events of thrombosis in early vascular graft. *Vassalli et al* in view of *Waugh et al* do not teach suppressing vascular thrombosis with I $\kappa$ B.

*Thomas et al* supplemented *Vassalli et al* in view of *Waugh et al* by establishing that it is well known in the art that I $\kappa$ B can enhance graft survival via interfering the early events of graft rejection, and by illustrating that I $\kappa$ B indeed enhances graft survival.

*Thomas et al* teach administering a NF- $\kappa$ B inhibitor DSG to suppress the inflammatory

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response to mismatched renal graft, and observed enhanced graft survival. *Thomas et al* also teach pre-treating the graft with the IκB.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method as taught by *Vassalli et al* in view of *Waugh et al* by further including an IκB in the Adv-TM for resisting early vascular graft failure as taught by *Thomas et al* with a reasonable expectation of success. The skilled in the art would have been motivated to do so for enhanced effect of suppressing vascular thrombosis. The skilled in the art would have had a reasonable expectation of success when combining the two agents, Adv-TM and an IκB, known to be effective for treating thrombosis when used separately. The ordinary skilled artisan would have had a reasonable expectation of success in inhibiting thrombosis of early vascular graft using the Adv-TM with or without an IκB, given the success of preventing thrombosis using Adv-TM alone as illustrated by *Waugh et al* or using the IκB alone as taught by *Thomas et al*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 53-55, and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Vassalli et al* (Cardiovasc Res 1997;35:459-69), in view of *Waugh et al* (Circ Res 1999;84:84-92, IDS) and *Thomas et al* (Transplant 1999;68:1660-73) as applied to claims 29-50, 52, 59, 60, 61 above, and further in view of *Hardy et al* (J Virol 1997;71:1842-9).

The combined teachings of *Vassalli et al* in view of *Waugh et al* and *Thomas et al*

do not discuss the specifics of the adenoviral vector, but such has been taught by *Hardy et al* and well known in the art. *Hardy et al* teach constructing an adenoviral vector comprising two ITRs and CMV promoter (e.g. fig. 1), and using such for cloning and expressing a therapeutic gene of interest.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the adenoviral vector as taught by *Hardy et al* in the method as taught by *Vassalli et al* in view of *Waugh et al* and *Thomas et al* with a reasonable expectation of success. Given the numerous expression vectors known in the art, these limitations fall within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 56-58, and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Vassalli et al* (Cardiovasc Res 1997;35:459-69), in view of *Waugh et al* (Circ Res 1999;84:84-92, IDS) and *Thomas et al* (Transplant 1999;68:1660-73) as applied to claims 29-50, 52, 59, 60, 61 above, and further in view of *Qing et al* (J Virol 1997;71:5663-7).

The combined teachings of *Vassalli et al* in view of *Waugh et al* and *Thomas et al* do not teach the specifics of a AAV vector, but such has been taught by *Qing et al* and well known in the art. *Qing et al* teach constructing an AAV vector comprising a RSV ITR promoter and using such for expressing a therapeutic gene (e.g. figure 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the AAV vector as taught by *Qing et al* in the method as taught by *Vassalli et al* in view of *Waugh et al* and *Thomas et al* with a reasonable expectation of success. Given the numerous expression vectors known in the art, these limitations fall within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ram R. Shukla** can be reached on 571-272-0735. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

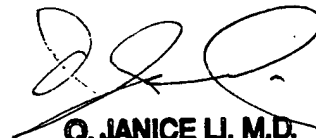
Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



**Q. JANICE LI, M.D.**  
**PRIMARY EXAMINER**

Q. Janice Li  
Primary Examiner  
Art Unit 1632

QJL  
March 21, 2005